REMARKS

Claims 8-16, 22, 23, 31, 43, 45 and 46 are presently pending. The Examiner indicated that Claim 45 was objected to as being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Amendments to Claim 8 are discussed below. Support for new Claim 46 is found in the specification as filed, for example in original Claim 3. New matter has been added herewith. The following addresses the substance of the Office Action.

Election/Restrictions

The Examiner indicated that Claims 10-15, 17-21 and 24-30 were drawn to nonelected species and that a complete reply to the Final Office Action must include cancellation of the nonelected claims or other appropriate action.

Applicant has canceled Claims 17-21 and 24-30. However, Claims 10-15 remain listed as withdrawn from consideration because Claim 8 is generic to these claims. Applicant understands that, upon allowance of a generic claim, Applicants should be entitled to consideration of claims to additional species (e.g., as listed in Claims 10-15), which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 C.F.R. § 1.141.

Obviousness

Langridge and Arakawa in view of Potter et al. and Tihova et al.

Claims 8, 9, 16, 22 and 43 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Langridge and Arakawa (U.S. Publication No. 2002/0055618 A1), Potter et al. (U.S. Patent No. 5,422,110) and Tihova et al. (2001 *J Mol Biol* **314**:985-992). Langridge and Arakawa teach the formation of various fusion proteins, which may contain different autoimmune autoantigens or pathogen autoantigens, such as VP4. The Examiner noted that Potter et al. teaches that VP4 or fragments thereof can be used in generating a fusion protein. Thus, one fusion protein option taught by Potter could contain the VP8 protein along with the remainder of the VP4 specific sequences if full-length VP4 was employed in the fusion protein.

To clearly distinguish over the teachings of the cited references, Applicant has amended Claim 8 by deleting recitation of "a fusion protein or fusion peptide comprising VP8 protein or a peptide derived from VP8." In addition, Claim 8 is amended to recite a protein or peptide

consisting of rotavirus VP8 protein, one or more peptide(s) derived fromVP8, or a mixture thereof. Thus, the closed terminology "consisting of" specifically limits the protein or peptide to a VP8 peptide, one or more peptide(s) derived from VP8, or a mixture thereof.

Referring to Examples 1-6 of the present specification, the Applicant has discovered that that rotavirus VP8 protein and peptides derived from VP8 protein induce the opening of tight junctions between epithelial and endothelial cells, thereby enhancing passage of therapeutic agents through epithelia and endothelia. The inventors identified domains present in VP8 that resemble the extracellular loops of the tight junction (TJ) proteins occludin and claudin. The inventors discovered that the VP8 protein and peptides derived from VP8 that bear a ≥50% similarity to the extracellular loops of claudin and occludin significantly reduce the transepithelial electrical resistance (TER) of Madin-Darby Canine Kidney (MDCK) cells. Example 1 of the present specification discloses that VP8 significantly reduces the TER of epithelial monolayers and Example 2 shows that VP8 modifies the cell border by changing the distribution of tight junction proteins. Example 5 shows that peptides derived from VP8, such as SEQ ID NO: 3 ($VP8_{141-182}$) and SEQ ID NO: 7 ($VP8_{183-186}$), significantly reduce the TER of epithelial cells. Example 6 demonstrates that when insulin is administered together with VP8, blood glucose concentration in diabetic rats diminishes significantly. Thus, the Applicant has determined that VP8 protein and peptides derived from VP8 induce opening of tight junctions between epithelial or endothelial cells, thereby enhancing passage of a therapeutic agent through epithelia and endothelia.

The Examiner noted at page 6, first full paragraph of the Office Action that the features of targeting of tight junctions/occludens and claudens by VP8 in order to enhance the passage of therapeutic agent through epithelia and endothelia were not recited in the claims. Applicant has amended Claim 8 to specifically recite "wherein said protein or peptide induces opening of tight junctions between epithelial or endothelial cells, thereby enhancing passage of said therapeutic agent through epithelia and endothelia." Based on the prior art of record, there was no reason or suggestion for the skilled artisan to believe that the presently claimed pharmaceutical compositions would be able to induce opening of tight junctions between epithelial or endothelial cells, thereby enhancing passage of said therapeutic agent through epithelia and endothelia.

Tihova et al. teaches that trypsin cleavage of rotavirus VP4 to yield VP8 and VP5 results in markedly increased infectivity by rotavirus. Thus, the Examiner concluded that one of ordinary

skill in the art would have had a reasonable expectation of success in generating a delivery agent containing the VP8 protein and a therapeutic agent for delivery of the agent to epithelia or endothelia due to the recognized involvement of rotavirus VP8 in the targeting of extracellular molecules during viral entry of the target cell. However, when VP8 facilitates increased viral infectivity, it is attached to an infectious rotavirus. When virus-bound VP8 protein binds to a cell receptor and mediates membrane permeabilization, cell entry by the associated rotavirus is facilitated. In contrast, the therapeutic agent in the presently claimed pharmaceutical composition is not necessarily attached to the VP8 protein or one or more peptide(s) derived from VP8. Accordingly, based on the teachings of Tihova et al., there could have been no reasonable expectation of success in enhancing delivery of such a therapeutic agent through epithelia and endothelia by the presently claimed pharmaceutical composition.

In view of the amendments to the Claims and the foregoing remarks, the claims are not *prima facie* obvious over the cited reference. Accordingly, the Applicant respectfully requests that the rejection be withdrawn.

Langridge and Arakawa in view of Potter et al., Tihova et al. and Honeyman et al.

Claims 23 and 31 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Langridge and Arakawa (*supra*), Potter et al. (*supra*), Tijova et al. (*supra*) and Honeyman et al. (2000 *Diabetes* **49**:1319-1324). However, since Claims 23 and 31 are ultimately dependent on Claim 8, and Honeyman et al. does not fill the gap between the teachings of Langridge and Arakawa, Potter et al. and Tijova et al. and the presently claimed compositions, Claims 23 and 31 are also not *prima facie* obvious. Accordingly, the Applicant respectfully requests that the rejection be withdrawn.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of Applicants' amendments to the Claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 14, 2011

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